Introduction:

Malaria is caused by the Plasmodium parasite transmitted by the anopheles mosquito. There are approximately 1,700 cases of malaria reported every year in the United States. And approximately 3.2 billion people live in areas at risk for malaria transmission in 106 countries and territories. Malaria can cause high morbidity and mortality, therefore, it should be strongly considered in patients coming from endemic countries or returning travelers from high risk areas.

There are five known species of Plasmodium including *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Depending on species, incubation period ranges from 10-14 days (*P. falciparum*) up to several months (*P. vivax*, *P. ovale*, etc.) after exposure to parasite from mosquito bite. Malaria usually presents with fever, chills, weakness, malaise, myalgia, nausea, vomiting, diarrhea, cough, headache, back pain, and confusion. In severe cases, it can also cause organ failure, coma, and death.

Diagnosis:

Primary diagnosis is made microscopically by thin and thick blood smears. Thick smears help with initial diagnosis due to the higher volume of blood, which increases sensitivity. Thin smears are useful in identification and quantification of the parasite. Ideally three sets of blood smears obtained every 12 to 24 hours help to increase sensitivity of the test especially for patients with low parasitemia. Three negative sets will rule out the diagnosis of malaria.

BinaxNOW, a rapid diagnostic test (RDT) is used at our institution. It can detect two malaria antigens. One antigen for all plasmodium species, and the second antigen is specifically for *P. falciparum*. Results are available in 15 minutes and will be reported as positive if *P. falciparum*, or possible co-infection with multiple species, or non-*plasmodium falciparum* infection is present. The sensitivity of the test for *P. falciparum* is 99.7% and specificity is 94.2%. This test CANNOT inform about percentage of parasitemia. The RDT is performed as reflex test in the laboratory in all the cases suspected for malaria with negative smears. For any questions regarding test results, please page Moses microbiology supervisor at 917-956-3012 from 9 am-5 pm, or page pathology resident on call from 5 pm-9 am.

Treatment:

Treatment is started after confirming diagnosis ideally, but it should be given presumptively when there is a high clinical suspicion of malaria, especially if the patient meets criteria for severe disease. Treatment options are guided by 1) species of Plasmodium 2) percentage of parasitemia 3) clinical status 4) history of prior use of antimalarial medications and presumptive drug susceptibility
Malaria Treatment Guideline for Adults (Adapted from CDC guidelines, modified to MMC formulary)

Based on area where infection was acquired. Chloroquine sensitive regions are Central America west of Panama Canal, Haiti, the Dominican Republic, and most of the Middle East. For further information of the list of chloroquine sensitive regions, please visit cdc.gov/malaria.

Treatment issues to consider:

1) **Plasmodium species**: *P. falciparum and P. knowlesi* are known to cause severe disease. Majority of cases of *P. falciparum* come from Sub-Saharan Africa. *P. knowlesi* is only reported in Malaysia and rarely seen. *P. ovale* and *P. vivax* can have liver dormant forms called hypnozoites that require specific treatment (see treatment tables).

2) **Clinical status**: Malaria is classified as uncomplicated or severe disease. Recognition of severe malaria is essential when choosing the appropriate treatment regimen. **Severe malaria is defined as one or more of the following criteria and requires intravenous treatment.** *(Note: for patients who are classified as uncomplicated malaria but unable to tolerate oral medications due to nausea or active vomiting, IV therapy should be administered.)*

<table>
<thead>
<tr>
<th>Severe Malaria Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired Consciousness/coma</td>
</tr>
<tr>
<td>Hemoglobin &lt;7 (consider hemoconcentration)</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Spontaneous bleeding</td>
</tr>
<tr>
<td>Acidosis (severe disease with HCO3 &lt; 15)</td>
</tr>
<tr>
<td>Hemoglobinuria</td>
</tr>
<tr>
<td>Jaundice</td>
</tr>
<tr>
<td>Repeated generalized convulsions</td>
</tr>
<tr>
<td>Parasitemia ≥5%</td>
</tr>
</tbody>
</table>

3) **Resistance**: pattern of resistance can vary according to different geographic regions for *P. falciparum* and *P. vivax*.

4) If malaria disease occurs despite the use of chemoprophylaxis, the **same medication should NOT be used** as part of the treatment. If there is difficulty identifying species once malaria diagnosis is made, treatment for possible chloroquine resistant *P. falciparum* is recommended.

**According to epidemiology data provided by the Montefiore microbiology lab**, a total of 114 malaria cases were reported between May 18th 2014 to February 2nd 2018 from inpatient services and outpatient clinics at Montefiore. Among these cases, **104 (91.2%) cases were P. falciparum**.
Malaria Treatment Guideline for Adults (Adapted from CDC guidelines, modified to MMC formulary)

**What history is important to obtain from patient?**

- What is the patient’s country of origin and when was the last time patient visited the country?
- Which country or countries did the patient travel to? How long was the stay? What date did the patient return from an endemic region?
- Did the patient take prophylaxis? If so, which medications? Was the patient compliant?
- Does the patient have previous history of malaria?
- Can the patient take oral medications?

**What labs are needed to help determine the severity of malaria illness?**

- Serial CBC (to monitor hemoglobin and platelets)
- Serial Chemistry
  - BUN/Creatinine- evaluate renal function
  - Bicarbonate and lactate- evaluate presence of acidosis
  - Bilirubin and LDH- evaluate for hemolysis
- **Bicarbonate < 20 is concerning**, consider placing patient in a highly monitored setting; must repeat labs to see the trend within 4 to 6 hours.
- Serial blood smears to speciate and obtain parasitemia percentage. BinaxNOW (quick diagnostic antigen test) will help you differentiate *P. falciparum* from *non-falciparum*. Please follow percentage of parasitemia every few hours to make sure it is declining

**Considerations when choosing treatment**

Treatment is primarily based on plasmodium species, percentage of parasitemia and clinical severity (see treatment tables). **For severe infection with any type of plasmodium species, IF appropriate intravenous therapy is delayed, give one dose of oral coartam until intravenous therapy can be initiated.**

*MMC Dosing of quinine, chloroquine and hydroxychloroquine are based on the salt formulation (see ancillary table on p.8)*

See page 9 for renal dose adjustments
<table>
<thead>
<tr>
<th>Plasmodium Falciparum Treatment or for species not yet identified</th>
<th>Chloroquine-resistant or Unknown Resistance (All countries known to have malaria are chloroquine resistant except the countries listed as chloroquine sensitive)</th>
<th>Chloroquine-sensitive (Central America west of the Panama Canal, Haiti, Dominican Republic, Middle East) For updates in malaria sensitivities check cdc.gov/Malaria</th>
</tr>
</thead>
</table>
| **Uncomplicated Malaria** | 1) **Quinine sulfate + either doxycycline or clindamycin** (quinine sulfate combination with doxycycline is preferred)  
Dose: Quinine 648 mg salt (two 324 mg salt-capsules = 542 mg base) PO Q8 H x 3 days (7 days if infection is acquired in South East Asia)  
+  
Doxycycline³ 100 mg PO Q12 H x 7 days  
Or  
Clindamycin 20 mg/kg/DAY PO divided in 3 doses x 7 days  
**OR**  
2) **Artemether-lumefantrine (Coartem)**  
Dose for >35 kg patient weight: 4 tablets at initial dose, then in 8 hours give 4 tablets followed by 4 tablets Q12 H x 2 days (total of 6 doses = 24 tablets)  
-Artemether-lumefantrine or quinine plus doxycycline or clindamycin are equivalent options  
-See footnote⁴ for other alternative options | 1) **Chloroquine phosphate**  
Dose: 1000 mg salt (two 500 mg salt-tablets = 600 mg base) initial dose PO followed by 500 mg salt (= 300 mg base) PO at 6, 24, and 48 hours for a total dose of 2500 mg salt (= 1500 mg base)  
**OR**  
2) **Hydroxychloroquine** (if chloroquine not available)  
Dose: 800 mg salt (four 200 mg salt-tablets = 620 mg base) initial dose PO followed by 400 mg salt (two 200 mg salt-tablets = 310 mg base) PO at 6, 24 and 48 hours for a total dose of 2000 mg salt (= 1550 mg base)  
-Chloroquine and hydroxychloroquine are equivalent alternatives |
| **Uncomplicated Malaria/Plasmodium falciparum in PREGNANCY⁵** | 1) **Quinine sulfate + Clindamycin**  
Dose: Quinine 648 mg salt (two 324 mg salt-capsules = 542 mg base) PO Q 8 H x 3 days (7 days if infection is acquired in South East Asia)  
+  
Clindamycin 20 mg/kg/DAY PO divided in 3 doses x 7 days  
-Mefloquine⁶ is another option for pregnant females. It’s a non-formulary medication and less frequently used due to CNS and psychiatric side effects. | 1) **Chloroquine phosphate**  
Dose: 1000 mg salt (two 500 mg salt-tablets = 600 mg base) initial dose PO followed by 500 mg salt (= 300 mg base) PO at 6, 24, and 48 hours for a total dose of 2500 mg salt (= 1500 mg base)  
**OR**  
2) **Hydroxychloroquine** (if chloroquine not available)  
Dose: 800 mg salt (four 200 mg salt-tablets = 620 mg base) initial dose PO followed by 400 mg salt (two 200 mg salt-tablets = 310 mg base) PO at 6, 24, and 48 hours for a total dose of 2000 mg salt (=1550 mg base)  
-Chloroquine and hydroxychloroquine are equivalent alternatives |

1. Treat for *P. falciparum* if species of plasmodium is not yet specified at time of diagnosis.  
2. If a patient develops malaria while taking chemoprophylaxis, the same medication should *NOT* be chosen for treatment  
3. In pregnancy: DO NOT use doxycycline (only can be used if no other options are available). There are no sufficient data for atovaquone-proguanil & artemether-lumefantrine during 1st trimester of pregnancy.  
4. Atovaquone-proguanil and mefloquine are alternative options (they are non-formulary medications). Avoid mefloquine use due to CNS and psychiatric side effects.  
5. Mefloquine should not be used in patients acquiring infection in South East Asia due to resistance and it is less commonly used due to psychiatric side effects.  

For any questions regarding test results, please page Moses microbiology supervisor at 917-956-3012 from 9am-5pm, or page pathology resident on call from 5pm-9am. For any questions regarding medications, please call pharmacy: Moses at 718-920-4103, Weiler at 718-904-2838 and Wakefield at 718-920-9631.
## Malaria Treatment Guideline for Adults (Adapted from CDC guidelines, modified to MMC formulary)

### Severe Malaria

- Severe disease can be caused by any species of *Plasmodium*
- Treat pregnant females as severe disease
- Severe malaria treatment criteria is independent from region where infection was acquired
- Infectious Disease team MUST be consulted for severe malaria

### In cases where initiation of appropriate intravenous therapy is delayed, give coartam until intravenous therapy can be initiated. This will NOT interfere with IV quinidine loading.

1) **IV Quinidine gluconate + doxycycline or clindamycin**

Quinidine gluconate: loading dose 10 mg salt/kg (6.25 mg base/kg) IV over 1-2 hours, then 0.02 mg salt/kg/min (0.0125 mg base/kg/min) continuous infusion for at least 24 hours. (Please do calculation based on salt dose)
- Quinidine gluconate is cardiotoxic leading to QTc prolongation and ventricular arrhythmias and can also cause hypotension and hypoglycemia. Patient requires ICU admission for monitoring. Please also see appendix.
- There is no maximum quinidine gluconate dose for treatment of Malaria.

**+**

- Doxycycline\(^2\) 100 mg Q12 H x 7 days (IV only if cannot tolerate PO)

**Or**

- Clindamycin 20 mg/kg/DAY PO divided in 3 doses x 7 days (IV only if cannot tolerate PO)

**Once parasitemia is <1%, can change IV therapy to oral quinine as detailed above. Total course of quinidine/quinine is of 3 days, but 7 days if infection was acquired in South East Asia.**

**OR**

2) **IV Artesunate:**

Dose: 2.4 mg/kg IV given as initial dose, then at 12 hours, and then every 24 hours for a total of 4 doses over 3 days

*A Artesunate is followed by doxycycline (use clindamycin if patient is pregnant), see doses and duration as recommended in *P. falciparum* chloroquine-resistant section.

**Choose IV artesunate if IV quinidine is unavailable, or there are contraindications for IV quinidine use, or parasitemia is >10% of baseline at 48 hours after starting IV quinidine.**

**Artesunate is an investigational drug, please call CDC Malaria Hotline: (770)488-7788 or (855) 856-4713 Monday-Friday 9am-5pm EST-{(770)488-7100 after hours, weekends and holidays**

**- Please register IV artesunate use for emergency use of an investigational drug via iRIS**

**- See footnote\(^6\) for other alternative options**

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6. Artesunate can also be followed by atovaquone-proguanil or mefloquine (they are both non-formulary).

7. Mefloquine should not be used in patients acquiring infection in South East Asia due to resistance; it is less commonly used due to CNS and psychiatric side effects.

For any questions regarding test results, please page Moses microbiology supervisor at 917-956-3012 from 9am-5pm, or page pathology resident on call from 5pm-9am. For any questions regarding medications, please call pharmacy: Moses at 718-920-4103, Weiler at 718-904-2838 and Wakefield at 718-920-9631.
### Malaria Treatment Guideline for Adults (Adapted from CDC guidelines, modified to MMC formulary)

<table>
<thead>
<tr>
<th>Treatment of Uncomplicated malaria for species other than <em>Plasmodium falciparum</em></th>
<th>Chloroquine-resistant</th>
<th>Chloroquine-sensitive</th>
</tr>
</thead>
</table>
| *Plasmodium malaria* or *knowlesi* | Given no concern for chloroquine resistance for these species, please see treatment for chloroquine sensitive *P. malaria* or *P. knowlesi* | Chloroquine phosphate  
Dose: 1000 mg salt (two 500 mg salt-tablets = 600 mg base) initial dose PO followed by 500 mg salt (= 300 mg base) PO at 6, 24, and 48 hours for a total dose of 2500 mg salt (= 1500 mg base)  
OR  
Hydroxychloroquine (if chloroquine not available)  
Dose: 800 mg salt (four 200 mg salt-tablets = 620 mg base) initial dose PO followed by 400 mg salt (two 200 mg salt-tablets = 310 mg base) PO at 6, 24, and 48 hours for a total dose of 2000 mg salt (= 1150 mg base)  
-Chloroquine and hydroxychloroquine are equivalent alternatives. Treatment options for chloroquine resistant *P. falciparum* also can be used. | (Central America west of the Panama Canal, Haiti, Dominican Republic, Middle East) |
| *Plasmodium ovale* | Given low concern for chloroquine resistant *P. ovale*, use chloroquine sensitive *P. ovale* treatment options | Chloroquine phosphate (dosing as above) + Primaquine phosphate: 30 mg base PO daily x 14 days (two 26.3 mg-tablets = 30 mg base)  
OR  
Hydroxychloroquine (if chloroquine not available) (dosing as above) + Primaquine phosphate: 30 mg base PO daily x 14 days (two 26.3 mg-tablets = 30 mg base)  
-MUST Check for G6PD deficiency prior to starting primaquine due to risk of hemolytic anemia | |
| *Plasmodium vivax* | If patient acquired infection in Papua New Guinea or Indonesia  
Quinine sulfate + doxycycline (dosing as in *P. falciparum* chloroquine resistant treatment section)  
+  
Primaquine phosphate: 30 mg base PO daily x 14 days (two 26.3 mg-tablets = 30 mg base)  
See footnote for alternative options | Chloroquine phosphate (dosing as above)  
OR  
Hydroxychloroquine (dosing as above)  
AND  
After completing treatment, patient should be maintained on chloroquine prophylaxis (ppx) for the duration of the pregnancy  
Chloroquine ppx dose is 500 mg (= 300 mg base) PO once a week  
AND  
After delivery and only if not G6PD deficient, start primaquine phosphate 30 mg base PO daily x 14 days (as detailed above) | |
| *Plasmodium ovale* and *vivax* in PREGNANCY  
-For *P. ovale*, always use chloroquine sensitive treatment options  
-For *P. vivax*, treat according to region where infection was acquired as recommended above | Quinine sulfate + clindamycin (for dosing and duration see *P. falciparum* and pregnancy section)  
AND  
After completing treatment, patient should be maintained on chloroquine prophylaxis (ppx) for the duration of the pregnancy  
Chloroquine ppx dose is 500 mg (= 300 mg base) PO once a week  
AND  
After delivery and only if not G6PD deficient, start primaquine phosphate 30 mg base PO daily x 14 days (as detailed above) | Chloroquine phosphate (dosing as above)  
OR  
Hydroxychloroquine (dosing as above)  
AND  
After completing treatment, patient should be maintained on chloroquine ppx for the duration of the pregnancy  
Chloroquine ppx dose is 500 mg (= 300 mg base) PO once a week  
AND  
After delivery and only if not G6PD deficient, start primaquine phosphate 30 mg base PO daily for 14 days (as detailed above) |

8. Primaquine + either atovaquone-proguanil or mefloquine are treatment options (they are non-formulary medications). Avoid mefloquine use due to CNS and psychiatric side effects.

9. For patients with borderline G6PD deficiency, consider treating with primaquine 45mg (3 tablets of 15 mg base) orally once a week x 8 weeks. For complete deficiency, do NOT use primaquine, and please monitor for signs and symptoms of reactivation of malaria to treat active disease.

10. Check G6PD deficiency for newborns prior to start treatment for mother because primaquine can be excreted in milk.

11. Mefloquine can be used in pregnant females (non-formulary medication). It’s less frequently used due to CNS and psychiatric side effects.

12. In pregnancy, DO NOT use primaquine and doxycycline (only can be used if no other options are available). There are no sufficient data for atovaquone-proguanil & artemether-lumefantrine during 1st trimester of pregnancy. For any questions regarding test results, please page Moses microbiology supervisor at 917-956-3012 from 9am-5pm, or page pathology resident on call from 5pm-9am. For any questions regarding medications, please call pharmacy: Moses at 718-920-4103, Weiler at 718-904-2838 and Wakefield at 718-920-9631.
Appendix

When Using IV Quinidine for Severe Malaria:

IV Quinidine is an older antiarrhythmic agent which is also used for severe malaria treatment. IV quinidine does not have a maximum daily dose recommended, dosing should be weight based and close cardiac monitoring is needed.

Baseline EKG and continuous cardiac monitoring (evaluate QTC, QRS) are required while patient is receiving IV quinidine. In addition, please also monitor blood pressure and electrolytes including serum potassium and magnesium concentrations (the goal is to maintain potassium >4.0 meq/liter and serum magnesium concentrations of >2.0 mg/dl).

Side effects to monitor:

- Cardiac signs of toxicity include: increase in QTc interval, QRS widening, ventricular arrhythmias, paradoxical tachycardia, and torsades de pointes. Also, can cause hypotension.

- Non-cardiac side effects: Include neurologic, gastrointestinal, hematologic, dermatologic complications. Important side effect is Hypoglycemia

What should I do, if there are cardiac complications from the medication?

- If QTC >600 ms → decrease infusion rate (can decrease to half of the dose)

- If QRS duration increase by 50%, QTC interval is > 25% from baseline or if become hypotensive not responsive to fluids → discontinue medication

- Beside Infectious disease specialist, cardiology needs to be consulted. If signs of cardiac toxicity need to contact the CDC for advice and consideration to start IV artesunate.

- Monitor for possible hypoglycemia. In order to prevent hypoglycemia, pharmacy will prepare quinidine IV with dextrose. Close glucose monitoring is still required. Non-cardiogenic pulmonary edema can occur even as parasitemia decreases leading to morbidity and extended ICU stay. This can be exacerbated by overhydration. Therefore, fluid hydration is recommended upon admission, but once the patient is euvoletic with matching I’s and O’s, strict input and output need to be monitored closely.
Ancillary Tables

**Malaria Medication/Strengths as per MMC Formulary:**

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine sulfate capsule</td>
<td>*324 mg salt (=269 mg base)</td>
</tr>
<tr>
<td>Artemether-lumefantrine (Coartem) tablet</td>
<td>20 mg artemether/120 mg lumefantrine</td>
</tr>
<tr>
<td>Chloroquine phosphate tablet</td>
<td>*250 mg salt (=150 mg base), 500 mg salt (=300 mg base)</td>
</tr>
<tr>
<td>Hydroxychloroquine tablet</td>
<td>*200 mg salt (=155 mg base)</td>
</tr>
<tr>
<td>Primaquine tablet</td>
<td>26.3 mg salt (=15 mg base)</td>
</tr>
</tbody>
</table>

*Dosing at MMC of quinine, chloroquine and hydroxychloroquine are based on salt formulation*
**Malaria Treatment Guideline for Adults (Adapted from CDC guidelines, modified to MMC formulary)**

**Renally Adjusted Antimalarial Medications Doses:**
For duration of treatment, please see full treatment tables.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether-lumefantrine (Coartem)</td>
<td>No adjustment. Use with caution in renal failure (has not been studied)</td>
</tr>
<tr>
<td>Artesunate</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>-CrCl &gt;10 ml/min or CRRT: no adjustment</td>
</tr>
<tr>
<td></td>
<td>-CrCl &lt;10 ml/min, HD or PD: 500 mg salt initial dose followed by</td>
</tr>
<tr>
<td></td>
<td>250 mg salt PO at 6, 24 and 48 hours</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Primaquine</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Quinidine (IV)</td>
<td>-In case of acute kidney failure, NO RENAL ADJUSTMENT needed.</td>
</tr>
<tr>
<td></td>
<td>-For chronic kidney disease:</td>
</tr>
<tr>
<td></td>
<td>-CrCl &lt;10 ml/min: loading dose 7.5 mg/kg salt IV over 1-2 hours,</td>
</tr>
<tr>
<td></td>
<td>then followed by 0.015 mg salt/kg/min continuous infusion for at least 24 hours</td>
</tr>
<tr>
<td></td>
<td>-HD: loading dose is unnecessary, start maintenance dose of 0.02 mg salt/kg/min</td>
</tr>
<tr>
<td></td>
<td>to be given after HD</td>
</tr>
<tr>
<td>Quinine</td>
<td>For mild to moderate malaria:</td>
</tr>
<tr>
<td></td>
<td>-GFR &gt;50 ml/min: no dose adjustment</td>
</tr>
<tr>
<td></td>
<td>-GFR 10-50 ml/min or CRRT: 648 mg salt Q8 or 12H</td>
</tr>
<tr>
<td></td>
<td>-GFR &lt;10 ml/min or PD: 648 mg salt Q24H</td>
</tr>
<tr>
<td></td>
<td>-HD: no dose adjustment needed, administered dose after hemodialysis</td>
</tr>
</tbody>
</table>

CRRT: continuous renal replacement therapy
PD: peritoneal dialysis
HD: hemodialysis